

FDA REVIEW OF THE PANRETIN RESPONDERS

PID	COMMENTS PROTEASE INHIBITOR (PI) EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE ³⁶ FDA REVIEW	BENEFICIAL RESPONSE
	No PI effect on response Maybe PI effect on <u>duration</u> of response Stable or decreasing CD4s during claimed initiation of response	No
	3 lesions raised @ baseline: flat	
	Listing: @ 2 wks 1 of the 3 became flat and a previously flat lesion (#6) became raise = 3 raised lesions	
	Listing:@ 12 wks or time of confirmation of response lesion #3 became nodular and increased in size	
	photos of lesions #1,#2, do not show benefit	
	Listing: flattening associated with erythema & edema	
	New lesions developing and growing despite gel (lower posterior global photos); may explain initiation of PI	
	Baseline photo for lesion #5 may be incorrect; photo provided looks like mid arm, subsequent photos look like wrist which is where lesion is suppose to be	
	baseline photo for lesion #5 appears incorrect; Ligand response: photo correct but wk 10 for lesions #4 & #5 are reversed	
	No PI effect	Yes
	3 raised lesion @ baseline: 2 of the 3 lesions became flat with onset of erythema and edema; area	

³⁶ Lesion (plaque or nodule) reduction in height = flat; lesion area reduction = area

PID	COMMENTS PROTEASE INHIBITOR (PI) EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE ²⁴ FDA REVIEW	BENEFICIAL RESPONSE
	marginal evidence of flattening of lesions	
	lesions #5 & #6 which in the listings disappeared, photo: erythema, edema, and skin reaction obscured lesion	
	2 of responding lesions became raised @ 16 wks; not confirmed in 1 month because pt did not come back; QOL deteriorated about this time	
	No PI effect	No
	6 nodular lesions: all 6 lesions became plaques	
	reduction from nodular to plaque associated with erythema and edema	
	photos of lesions do not show benefit	
	either new lesions appearing and treated on back of right leg as early as 4 wks or lesions not mapped @ baseline	
	QOL & PGA agree with above	
	No PI effect; slowly increasing CD4 & triglycerides after response, suggest change in PI	No
	6 raised lesions: all 6 lesions became flat	
	No baseline index lesions photographs x 6; Ligand response: photos overexposed	
	no 8 wk photos; Ligand response: photos rendered a very light exposure; Ligand correct: poor quality photos	
	no 4 wk photo for lesion # 6; from lower posterior global photo it looks worse	
	globally lesions disappear @ 18 wks	
	photos of lesions do not show benefit	

PID	COMMENTS PROTEASE INHIBITOR (PI) EFFECT CHARACTER OF LESIONS & REPORTED RESPONSE ²⁴ FDA REVIEW	BENEFICIAL RESPONSE
	No PI effect PI effect after response started lesions start to disappear after crixivan started	Yes
	3 raised lesions became flat; area	
	Pt. Stopped & refused panretin when switched to crixivan; this explains lack of erythema in lesions after crixivan	
	Lesions on back appear not to have been treated	
	lesions on back disappearing after crixivan started; pt. does have a history of acne on the back: no specific Rx indicated, except for Westcort creme. Ligand response: Westcort creme applied to forehead, neck, upper arms, & medial thighs (no mention of back).	
	index lesions do not show reaction after 4 wks; a few show fading reaction	
	flattening associated with erythema and edema	
	above explains PGA and patient not impressed	
	No PI effect new lesions continue after crixivan new lesions stop & start to disappear (lower post. legs) after nelfinavir started	No
	3 raised lesions became flat	
	new lesions @ 4 wks right lower posterior leg	
	new lesions @ 8 wks right and left lower posterior legs	

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	flattening associated with erythema and edema	
	photos of lesions do not show benefit	
	when new lesions on legs started to disappear, treated index lesions persisted	
	No PI effect	No
	4 lesions raised: 2 lesions became flat	
	gel did nothing for other 4 lesions	
	photos of lesions do not show benefit	
	lesions (2) on the feet that became flat--> cannot tell by photos that anything at all happened except some edema.	
	No PI effect	Yes
	3 raised lesions + 1 nodular; all became flat; area; CR	
	photos of lesions do not show CR	
	With as dramatic of a response as this patient had, why were only 6 of 10 lesions treated?	
	No PI effect	Yes
	5 raised lesions: all became flat; area	
	Lesions #1 & #2, @ 8 wks measurable and not measurable, resp.; photos look the same	
	photos of lesions show benefit	
	No PI effect but CD4 increased 3-fold;	Yes

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	Ligand response: patient did not receive protease inhibitors, prior to study or during the study	
	3 lesions raised + 1 lesion nodular: all became flat; area	
	Flattening associated with erythema and edema	
	No 4 wk evaluation with photos; Ligand response: no photos taken @ wk 4	
	area reductions in lesions #1, #3, #4, & #5 are not evident	
	photos of lesions show benefit	
	No PI effect	No
	5 raised lesions: all became flat; area	
	No baseline photos. Ligand response: baseline photos were not taken	
	lesions #1 & #2: flattening associated with edema; area reduction not clear	
	The rest of lesions do not show clear flattening or reduction in area	
	lesion #6 looks improved @ 21 wks; no baseline and no confirmation	
	No PI effect: CD4 decreased	No
	3 raised lesions: all 3 became flat; area	
	Follow up and confirmation photos missing, specifically, weeks 4 & 8 and weeks > 12; Ligand response: week 4 photos useless, week 8 photos not taken: Ligand correct: poor quality photos	
	no follow up photos for lesion #6; Ligand response: wk 4 useless, no wk 8	

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	photos taken, and patient missed wk 16	
	Appears that all lesions not mapped; lesions on right upper chest, post. arms and legs	
	Post. arms do not appear to have had gel applied; no lesions @ 12 wks: PI effect?	
	Flattening appears associated with erythema and edema	
	Photos do not demonstrate flattening in 3 raised lesions	
	No PI effect	Yes
	6 raised lesions: all became flat; area	
	3 index lesions on head and no baseline view of head	
	all index lesions: no baseline photos submitted; Ligand response: baseline photos over-exposed; Ligand correct: photos are poor quality	
	photos show changes in lesions, particularly 3 facial lesions	
	No PI effect	No
	4 raised lesions: all raised lesions became flat	
	no baseline photos; Ligand response: baseline photos over-exposed; Ligand correct: photos poor quality	
	incorrect photos for lesions #5 & #6 @ 4.4 wks; Ligand response: photos are reversed;	
	photos of lesions do not show benefit	
	No PI effect	Yes

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	5 raised lesions @ baseline: all became flat; area	
	global photos: poor quality	
	lesions #1 & #2 are responses; lesions #3 & #5 are responses but relapse @ 12 wks and not recorded in Listing as such; lesion #4: no response @ 8 wks as in Listing but response @ 12 wks (not confirmed)	
	PI effect	No
	3 lesions raised: all became flat	
	Many of index lesion measurements identical	
	Photos of lesions do not show benefit	
	no PI effect	No
	5 raised lesions: 4 became flat	
	bilat. Ankle edema @ baseline; edema in legs (photos) @ 4, 8, 12, & 17 wks; recorded in CRF wks 12 & 17; edema: adverse event for drug discontinuation	
	photos of lesions do not show benefit, especially when compared to global photos of the area treated	
	no PI effect: CD4s stable	No
	6 lesions raised: 5 became flat	
	Erythema not accurately recorded: lesion #1 scored as 0 @ wks 4 & 8, photo @ 6 wks marked erythema and edema; lesion #2 scored as 0 throughout,	

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	photos demonstrate marked erythema and edema	
	Flattening associated with erythema & edema	
	Photos of lesions do not show benefit	
	PI effect: inconclusive	No
	3 raised lesions: all became flat	
	Photos of lesions do not show benefit	
	PI effect: CD4s increased @ time of response	Yes
	6 raised lesions: all became flat	
	Response in lesions #1, #2, #3 (baseline not impressive), #6	
	Lesion #5 looks worse	
	Treated non-index lesions not impressive	
	No PI effect; stable CD4	Yes
	6 raised lesions: 5 became flat; area	
	lesions #1, #2, #3, #5 are responses	
	4 lesions demonstrated no erythema; the 2 other lesions had grade 1 erythema for 12 wks then none for the next 44 wks; Ligand response: pi was randomized to panretin	
	photos for lesion #2 have freckle (a landmark) with lesion @ baseline, 4 and 9 wks; subsequent photos do not have freckle in the photo; Location of KS	

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	lesions diagram does not match photos for lesions #2 & #3: reversed	
	No PI effect	Yes
	5 nodular lesions + 1 raised lesions: 4 nodular + the 1 raised became flat	
	Photos do not demonstrate nodular → flat in lesions #1, #3	
	KS Lesion Location in CRF for lesion #6 indicates left eyebrow—photos are of right eyebrow	
	Flattening associated with erythema & edema	
	No PI effect	No
	6 nodular lesions: 5 became raised	
	nodular was not representative of disease; pt. had patches of KS	
	Benefit of lesions changing from nodular to raised not obvious	
	PI effect; CD4 increased	No
	4 nodular + 2 raised lesions: all became flat except 1 nodular to raised; area	
	3 lesions became flat; only 5 instances of erythema out of a possible of 90 → cannot see erythema in non-index lesions for determination of PI vs panretin effect; from lower post. Photos: non-index lesions not responding	

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	No PI effect	Yes
	4 raised lesions: 3 became flat	
	Lesions #1,#2 are responses	
	Photographic evidence for benefit for other lesions not apparent: lesion #3 looks worse	
	No PI effect	Yes
	4 raised + 2 nodular lesions: 4 + 1 became flat, resp.	
	Erythema and edema associated with flattening	
	photos of lesions show benefit	
	No PI effect on response PI effect after crixivan started	Yes
	5 nodular + 1 raised lesions: all became flat	
	Erythema and edema associated with flattening	
	Photos of lesions show benefit	
	No PI effect	No
	3 nodular + 3 raised lesions: 1 + 2 became flat resp.	
	no erythema	
	No PI effect	No
	4 raised + 2 nodular lesions:	

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	all became flat	
	Photos of lesions do not show benefit	
	No PI effect	Yes
	3 raised lesions: area	
	Lesions #1 & #2 are responses	
	the surface area verified by photos	
	No PI effect	Yes
	4 nodular lesion + 1 raised lesions: 4 nodular lesions became raised	
	responses in lesions #2,#4,#6	
	no response apparent in lesions #1,#3	
	erythema and edema associated with flattening	
	No PI effect???	Yes
	3 raised lesions: all became flat	
	No response apparent in lesions #1,#2,#3 by photographs	
	Photos of lesions do show benefit	
	Prior flat lesion became raised @ time of response confirmation of flattening of other 3 raised lesions Surface area increased @ next visit	
	left leg cellulitis between wks 12 & 16; left was a site where non-index lesions treated with panretin; Ligand response: cellulitis probably related to study drug and reason for drug termination	

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	No PI effect	No
	4 raised lesions: all became flat	
	No photos of lower extremities	
	Lesions #4 & #5 are responses	
	Lesions #1 & #2 appear larger @ 8 wks	
	Lesion #3 cannot be discerned @ baseline; Ligand response (8/17/98): requesting confirmation from the site with regard to location of the lesion--Ligand believes lesion below 1st "7" in in-photo label; Ligand (10/9/98): Investigator: below "D" in-photo	
	No PI effect	No
	4 raised lesions: 2 became flat	
	Lesions #2 & #6 look like responses; no confirmation on response for #6-->patient died	
	Photos of lesions do not show benefit	
	No PI effect??	No
	3 raised lesions: 2 became flat	
	Photos of lesions do not show benefit or what listings describe	
	Erythema and edema associated with flattening	
	Lesions #, 1, #2, #4 are responses	
	Other lesions looked unchanged or worse	

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	No PI effect	Yes
	6 raised lesions: 4 became flat	
	Lesion #1 is response	
	nose lesion #2 response	
	nose lesion #3 on opposite side of nose did not respond	
	Lesion #4 response	
	Some lesions showed activity; others (e.g. #5 & #6) did not show activity— maybe look worse (e.g., #6)	
	PI effect?? Ligand claims that PI not changed or adjusted	Yes
	3 raised lesions: all became flat; area	
	Responses:#1,#3,#4; Questionable #5	
	No PI effect	No
	3 raised lesions: 1 became flat, 6 became nodular or a grade not specified in CRF ? (6 lesions scored as 3 which is not part of height scale on CRF) 1 raised lesion became flat then raised @ next visit	
	Cannot see responses in lesion #1, #2	
	Lesion #3 went from flat to nodular; not a response	
	Lesion #4 buried in erythema, edema, scab tissue	

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	Lesion #5 is not a response; very bad looking response	
	Lesion #6 is not a response	
	Erythema and edema associated with flattening	
	New lesions ~ 2 wks after wk 12 eval: prompted Rx with interferon	
	PI effect	Yes
	5 raised + 1 nodular lesion: all became flat	
	Lesion #1 is a response {	
	No PI effect	No
	6 raised lesions: all became flat	
	Lesion #1 is a response	
	#5 and #6 are marginal responses	
	Cannot see responses in lesions #2, #3, #4; except for 1 instance, no erythema	
	No PI effect	Yes
	6 raised lesions: 5 became flat	
	Responses in lesions #1, 2, 3, 4 not matured	
	Lesions #5 & #6 may be responses but not confirmed by photos; Ligand response: no photos after wk 8 & pt lost to follow up after wk 8	
	#5 & #6 globals suggest response; non-index lesions on lower back appear to be responding; no further followup	

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	photos; other lesions not responding	
	No PI effect	No
	6 raised lesions: 3 became flat	
	More lesions treated then reported	
	@ the 27th week either an index lesion was changed or a 7 th index lesion was added; Ligand response: extra lesion label on pt's anterior right upper arm	
	Lesion #1 @ week 23 and lesion #3 @ week 27 appear to be the same lesion if not the same photo. Ligand response: photo for lesion #1 wk 23 is correct. FDA: the photos for lesions #1 & #3 may have been reversed @ wk 27	
	Review of the global photos: for lesion #1 @ wk 23 the lesion cephalad (@ the nipple level) to the original lesion was labeled and photographed; @ wk 27 both the original #1 lesion and the new #1 lesion were labeled	
	Review of the global photos: for lesion #3 @ wk 27, the new lesion evaluated as lesion #1 @ wk 23 was evaluated as lesion #3	
	no response in lesions #1 & #3,	
	Lesion #2 is a response	
	Lesions #4-#6 did nothing; actually looks worse	
	Erythema and edema associated with flattening	
	No PI effect?	Yes
	6 nodular lesions: 5 became raised, 1 became flat	